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Functional network topology associated with posttraumatic stress disorder in veterans

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ABSTRACT

Posttraumatic stress disorder (PTSD) is a disabling disorder associated with resting state functional connectivity alterations. However, whether specific brain regions are altered in PTSD or whether the whole brain network organization differs remains unclear. PTSD can be treated with trauma-focused therapy, although only half of the patients recover after treatment. In order to better understand PTSD psychopathology our aim was to study resting state networks in PTSD before and after treatment. Resting state functional magnetic resonance images were obtained from veterans with PTSD (n = 50) and controls (combat and civilian controls; n = 54) to explore which network topology properties (degree and clustering coefficient) of which brain regions are associated with PTSD. Then, PTSD-associated brain regions were investigated before and after treatment. PTSD patients were subdivided in persistent (n = 22) and remitted PTSD patients (n = 17), and compared with combat controls (n = 22), who were also reassessed. Prior to treatment associations with PTSD were found for the degree of orbitofrontal, and temporoparietal brain regions, and for the clustering coefficient of the anterior cingulate cortex. No significant effects were found over the course of treatment. Our results are in line with previous resting state studies, showing resting state connectivity alterations in the salience network and default mode network in PTSD, and also highlight the importance of other brain regions. However, network metrics do not seem to change over the course of treatment. This study contributes to a better understanding of the psychopathology of PTSD.

1. Introduction

Posttraumatic stress disorder (PTSD) is a trauma- and stressor-related disorder that can develop after experiencing a traumatic event (American Psychiatric Association, 2013). Since many veterans are exposed to traumatic events during deployment, they are at risk for developing PTSD. About six to twelve percent of the veterans who have been deployed to Afghanistan and Iraq develop a high level of PTSD symptoms (Hoge et al., 2004; Reijnen et al., 2014). Trauma-focused therapy is shown to be an effective therapeutic strategy for PTSD, which stimulates fear habituation and induces fear extinction of trauma-related memories (Rothbaum and Davis, 2003). However, only half of the PTSD patients recover after trauma-focused therapy (Bradley et al., 2005). In order to improve response rates it is important to understand the psychopathology of PTSD, and to determine biological markers for treatment outcome. Therefore, we investigated neurobiological alterations in PTSD and controls in a longitudinal design, before and after trauma-focused therapy.

PTSD has been associated with hyperactivity of limbic brain regions, such as the amygdala, and hypo-activity of brain areas involved in emotional regulation, such as the ventromedial prefrontal cortex (vmPFC; (Liberzon and Sripada, 2007; Rauch et al., 2006). Over the last decade alterations in resting state functional connectivity have been reported in PTSD in cross-sectional studies. Resting state functional connectivity refers to a correlation between brain activation of different regions, indicating synchronization of neural activation of those regions during rest (Greicius et al., 2009). It has been suggested that alterations in two specific networks may underlie PTSD: the default mode network (DMN), and the salience network (SN; Daniels et al., 2010; Sripada et al., 2012b). The DMN is a network that is activated during rest, and consists of the medial prefrontal cortex, posterior cingulate cortex, precuneus and temporoparietal regions (Greicius et al., 2009; Raichle et al., 2001). The DMN is thought to be involved in autobiographical memory processes and self-referential processing (Kelley et al., 2002). The SN, including the dorsal anterior cingulate cortex (ACC) and insula as core nodes, has been associated with attentional processes (Seeley

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et al., 2007). Alterations in the DMN and SN have been reported during resting state in PTSD compared to non-trauma-exposed controls (Bluhm et al., 2009; Daniels et al., 2010), and trauma-exposed controls (Sripada et al., 2012b). However, alterations in functional connectivity between other regions are also found compared to non-trauma-exposed controls (Chen and Etkin, 2013; Kennis et al., 2014), and to trauma-exposed controls (Brown et al., 2014; Dunkley et al., 2014; Sripada et al., 2012a; Yin et al., 2011). Therefore, it remains unclear whether resting state functional connectivity is altered in the DMN and SN only in PTSD, or whether the whole brain network is altered. Moreover, it has been suggested that normalization of resting state network connectivity may be related to a reduction in (specific) PTSD symptoms (Lanius et al., 2015). For example, changes in arousal level may be related to alterations in a network including the insula and dorsal anterior cingulate cortex (ACC), and an altered sense of self can be related to alterations in a network including the medial PFC and posterior cingulate cortex (PCC; Tursich et al., 2015). However, the effect of treatment on resting state functional connectivity has not been investigated. Therefore, it is relevant to study which brain regions are in particular altered in PTSD, and if treatment effects functional connectivity of these regions.

Recently, functional magnetic resonance imaging (fMRI) studies have emerged investigating neurobiological effects of treatment in PTSD. Task-based activation studies reported pre-treatment differences in the prefrontal cortex, anterior cingulate cortex and amygdala activation that normalized to control levels after treatment (Fani et al., 2011; Felmingham et al., 2007; Roy et al., 2010; Simmons et al., 2013). Pre-treatment differences in hippocampal and anterior cingulate structure (Bryant et al., 2008a; van Rooij et al., 2015c) and amygdala, ACC and superior parietal lobule function (Aupperle et al., 2013; Bryant et al., 2008b; van Rooij et al., 2015b) have been shown to be markers of treatment outcome. This suggests that some neurobiological characteristics of PTSD may restore after treatment, while other features are stable markers for treatment outcome.

Here, we investigated resting state functional brain network topology in PTSD before and after treatment using graph theoretical analysis (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010). Graph theoretical analysis applied on whole brain resting state functional connectivity provides a data driven methodology for whole brain analyses, without specific a priori seed selection (Bullmore and Sporns, 2009; van den Heuvel and Hulshoff Pol, 2010). We investigate two basic network metrics that have a straightforward neurobiological interpretation: the degree and clustering coefficient. The degree of a brain region (a node) is the number of connections of a node, and represents the importance of a node in the network by functionally interacting with many other nodes (Rubinov and Sporns, 2010). The clustering coefficient reflects the interconnectedness of a group of nodes surrounding a node, and when this is high the nodes forms a cluster. A high clustering coefficient is indicative of functional segregation (Rubinov and Sporns, 2010). First, we investigated which whole brain functional network properties are associated with PTSD prior to treatment (baseline) using backward regression on PTSD patients and controls (including combat-exposed veteran controls and civilian controls). Based on previous resting state studies, we expected that network metrics of the amygdala, hippocampus, thalamus, insula, mPFC, PCC, and precuneus are associated with PTSD.

Second, a follow up scan was acquired for the patients and combat controls six to eight months after the first scan. During that interval PTSD patients received trauma-focused therapy. To investigate treatment effects we compared the network metrics associated with PTSD between patients who still had a PTSD diagnosis after treatment (persistent PTSD), patients who recover from PTSD (remitted PTSD), and combat controls. We expected to observe normalization of the network alterations to combat control levels in remitted PTSD patients, and treatment outcome-related differences.

2. Materials and methods

2.1. Participants

In total, 53 PTSD patients, 29 veteran controls (combat controls) and 26 civilian controls (healthy controls) were included, who were all male. Patients were recruited from one of four outpatient clinics of the Military Mental Healthcare Organization, The Netherlands. Patients were included after a psychologist or psychiatrist diagnosed PTSD. PTSD diagnosis was confirmed using the Clinician Administered PTSD scale (CAPS ≥45; Blake et al., 1995). The Structural Clinical interview for DSM-IV (SCID-I; First et al., 1997) was applied to diagnose comorbid disorders. A trained psychologist or PhD student administered the interviews. Control participants were recruited via advertisements, and the interviews (SCID and CAPS) were also applied to investigate PTSD symptoms and psychiatric disorders. Inclusion criteria for controls were no current psychiatric or neurological disorder, and no presence of current PTSD symptoms (CAPS ≤15).

After an interval of six to eight months 39 PTSD patients and 22 combat controls were reassessed with interviews and MRI. In order to match the civilian controls to the veteran groups on age, the civilian controls were recruited after the veterans. However, due to scanner updates during our protocol re-assessment of the civilian controls was not performed. Baseline and follow-up scans of the veteran groups were all performed before the scanner update. During the six to eight months interval patients received trauma-focused therapy, in line with Dutch and international treatment guidelines (Balkom et al., 2013; Bisson et al., 2007; Foa et al., 2000). Trauma-focused therapy included trauma-focused cognitive behavioral therapy (TFCBT) and/or eye-movement desensitization and reprocessing (EMDR), which are both effective therapeutic strategies that have similar efficacy (Bisson et al., 2007). A clinician applied the treatment (treatment as usual), and decided which strategy was applied initially. Based on PTSD diagnosis at the re-assessment according to DSM-IV criteria (American Psychiatric Association, 1994) PTSD patients were divided into a remitted group (no PTSD diagnosis at reassessment; n = 17), and a symptom persistent group (PTSD diagnosis at reassessment; n = 22). After receiving a complete written and verbal description of the study all participants gave written informed consent. The Medical Ethical Committee of the UMC Utrecht approved the study, and the study was performed in accordance with the Declaration of Helsinki (World Medical Association, 2013).

2.2. Image acquisition and pre-processing

Resting state functional magnetic resonance images were obtained on a 3.0 Tesla scanner (Philips Medical System, Best, the Netherlands: T2*-weighted echo planar interleaved images, repetition time TR = 1600 ms, TE = 23 ms, flip angle = 72.5°, field of view (FOV) 256 × 208 × 120, 30 transverse slices, 64 × 51 matrix, total scan time 8 min and 44.8 s, 0.4 mm gap, acquired voxel size 4 × 4 × 3.60 mm), where participants were asked to focus on a fixation cross, while letting their mind wander and relax. Images were pre-processed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/), and the Resting-State fMRI Data Analysis Toolkit (restfmri.net; Song et al., 2011). Pre-processing included slice-timing correction, realignment, co-registration with a T1-weighted high resolution scan acquired during the same scan session (TR = 10 ms, TE = 4.6 ms, flip angle 8°, 200 sagittal slices, FOV 240 × 240 × 160, matrix of 304 × 299), normalization, spatial smoothing (8 FWHM), de-trending, and band-pass filtering (0.01–0.08 Hz). Individuals that showed excessive motion (>2 mm in x, y, z direction or >2° in pitch, roll, yaw rotation) were excluded from analyses (three PTSD patients, one healthy control), resulting in baseline data of 50 PTSD patients and 54 controls, and data at reassessment of 39 PTSD patients and 22 combat controls. To correct for physiological noise and motion, nuisance parameters were included as regressors in the analyses (cerebrospinal fluid signal, white matter signal, and

individual realignment parameters). Using the automated anatomical labeling (AAL) template (Tzourio-Mazoyer et al., 2002), the mean time-series of 90 anatomical structures were extracted and correlated with each other (Pearson's correlation) to create individual subject correlation matrices. The cerebellar regions were excluded, since the cerebellum was not included in the FOV for all subjects. The correlation matrices were used for calculation of network measures.

2.3. Network metrics

Network metrics were calculated with the brain connectivity toolbox (https://sites.google.com/site/bctnet/Home; Rubinov and Sporns, 2010). The individual correlation matrices were thresholded over a range of initial height thresholds (ranging from 0 to 0.9 in steps of 0.1), where a 0.1 threshold indicates that only correlations higher than 0.1 are preserved in the weighted correlation matrix. The minimum threshold was 0 in order to circumvent interpreting negative correlations, which can be induced due to pre-processing steps (Van Dijk et al., 2010), and up to 0.9 since 1 is the maximum value of a correlation coefficient. Several thresholds were investigated to prevent bias of selecting one threshold. For each of the matrices node-specific degree and clustering coefficient were calculated (undirected). These network metrics were chosen since they are basic graph metrics that have a straightforward neurobiological interpretation (Rubinov and Sporns, 2010). The degree of a node is the number of connections of a node that link the node to the rest of the network, indicating the importance or centrality of a node in the network (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010). The clustering coefficient is the number of connections to the nearest neighbors of a node as a fraction of the maximum number of possible connections between the nearest neighbors, which is a measure of functional segregation (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010).

2.4. Network statistics

To explore which pre-treatment (baseline) network properties were related to PTSD, backward Wald regression was applied (IBM SPSS statistics version 21). Backward Wald regression determines the most optimal fitted model, with a minimum number of variables, which best explains the factor of interest (group: PTSD versus non-PTSD). The veteran (trauma-exposed) and civilian (non-trauma-exposed) controls were not investigated as separate groups, since we were not interested in the effects of trauma exposure in particular, but in PTSD-related characteristics. Therefore we investigated PTSD patients versus all controls combined. Backward regression also provides a data-driven method without a priori specified variables of interest. To circumvent colinearity the left and right hemisphere were analyzed separately, as well as the degree and clustering coefficient. In a case where the model did not run due to convergence of the variables in the algorithm, one of two variables with the highest correlation was removed from the regression model, and regarded as representing both variables in the final model. Bonferroni correction was applied for the number of backward regression models investigated ($p < 0.05/40 = 0.00125$ is deemed significant). The brain regions that were consistently associated with PTSD in the optimal fitted model over at least four height thresholds were further investigated over the course of treatment. A minimum of four thresholds was chosen to reduce false positives found (e.g. results for a single threshold), and to reduce bias by selecting one representative threshold, but also to retain sensitivity for detecting connectivity variables related to PTSD. Of note, the method of thresholding and reporting results over thresholds remains subject of discussion, and optimal procedures should be developed in order to standardize analysis methods (Drakesmith et al., 2015). To give an indication for the direction of the relation the mean b-value was calculated. For these regions repeated measure ANOVA's were utilized to assess treatment-related changes over time between remitted and persistent PTSD patients and combat controls (3 groups × 2 time points). Bonferroni correction was applied to correct for the number of brain regions that were investigated. Furthermore, correlational analyses between symptom improvement (ΔCAPS = baseline CAPS − reassessment CAPS) and change in network characteristics for the PTSD associated brain regions were explored within the PTSD group.

3. Results

3.1. Demographics

An overview of the demographical and clinical data can be found in Tables 1 and 2. Age and handedness did not differ between PTSD patients (n = 50) and controls (n = 54; see Table 1). Educational level as measured with the international standard classification of education (ISCED; Schneider, 2013) was higher in controls than in PTSD patients, but parental education did not differ. Early life trauma was also higher in PTSD patients, which was driven by the civilian controls, who reported the lowest early trauma experiences. PTSD severity as measured with the CAPS was higher in PTSD patients than in controls.

At the reassessment, 17 PTSD patients were remitted and 22 still had a PTSD diagnosis, in line with previously response rates of 50% (Bisson et al., 2013). The remitted and persistent PTSD patients and combat controls (n = 22) did not differ in age, education, handedness, early life trauma, number of times deployed, time since last deployment, or time between scans (see Table 2). The remitted and persistent PTSD groups showed no difference in number of treatment sessions, and psychotropic medication (see Table 2). About a third of the patients was taking psychotropic medication at baseline, mostly selective serotonin reuptake inhibitors (SSRI) and benzodiazepines. After six to eight months, more persistent PTSD patients were using prescribed medication. Persistent PTSD patients had more comorbid mood disorders at baseline, and more comorbid anxiety disorders at both time points. At baseline persistent PTSD patients showed a trend significant higher symptom severity compared to remitted PTSD patients.

Table 1
Demographical characteristics for PTSD patients and controls at baseline. ISCED = international standard classification of education; CAPS = clinician-administered PTSD scale; SSRI = selective serotonin re-uptake inhibitor; SARI = serotonin antagonist and reuptake inhibitor.

	PTSD (mean ± SD)	Controls (mean ± SD)	Test-value (df)	*p*-Value
Number of participants	50	54		
Veterans/civilian	50/0	29/25		
Age (range 21–57)	36.30 (±9.64)	35.74 (±9.68)	$t_{(102)} = -0.29$	0.769
Education (ISCED)				
Own	3.80 (±1.24)	4.53 (±1.58)	$t_{(98)} = 2.59$	0.010
Mother	2.54 (±1.35)	3.02 (±1.63)	$t_{(98)} = 1.60$	0.114
Father	3.50 (±1.92)	3.28 (±1.82)	$t_{(97)} = -0.58$	0.566
Edinburgh handedness inventory (left/ambidextrous/right)	(4/4/41)	(2/4/48)	$\chi^2_{(2)} = 0.98$	0.614
Early trauma inventory	4.82 (±4.57)	2.58 (±2.04)	3	0.005
CAPS total score	70.44 (±13.42)	5.06 (±4.56)	$t_{(102)} = -32.75$	$p < 0.001$

Table 2
Demographical and clinical characteristics of combat controls, remitted PTSD and persistent PTSD at baseline and at the reassessment.

	Remitted PTSD (mean ± SD)	Persistent PTSD (mean ± SD)	Combat control (mean ± SD)	Test-value (df)	*p*-Value
Number of participants	17	22	22		
Age (range 21–57)	35.12 (±9.53)	38.82 (±9.74)	36.73 (±10.67)	$F_{(2,58)} = 0.67$	0.516
Education (ISCED)					
Own	3.88 (±1.27)	3.55 (±1.14)	4.14 (±1.67)	$F_{(2,58)} = 1.00$	0.374
Mother	2.44 (±0.73)	2.48 (±1.66)	3.18 (±1.47)	$F_{(2,56)} = 1.86$	0.165
Father	3.41 (±1.66)	3.60 (±2.56)	3.90 (±1.84)	$F_{(2,55)} = 0.31$	0.732
Handedness (left/ambidexter/right)	(1/0/16)	(3/2/17)	(2/2/18)	$\chi^2_{(4)} = 2.17$	0.700
Early trauma inventory					
Number of times deployed (1/2/3/>3)	(4/4/4/5)	(9/3/6/3)	(7/6/4/5)	$F_{(2,57)} = 0.88$	0.420
Time since last deployment (years)	6.53 (±7.95)	8.86 (±9.31)	5.95 (±6.83)	$F_{(2,57)} = 0.78$	0.464
Country of last deployment	3.50 (±3.06)	5.43 (±5.04)	2.95 (±2.82)	$F_{(2,57)} = 2.39$	0.102
Afghanistan	12	12	15		
Former Yugoslavia	2	6	4		
Other	3	3	3		
Time between scans in (months)	6.12 (±1.11)	6.23 (±1.07)	6.32 (±0.48)	$F_{(2,58)} = 1.88$	0.161
Total trauma-focused treatment sessions between assessments (<5/5–10/>10)	9.18 (±6.78) (4/7/4)	9.50 (±4.88) (3/10/10)		$t_{(37)} = -1.73$	0.863
Clinical scores at baseline					
PTSD severity (CAPS total score)	65.00 (±12.45)	72.95 (±14.39)		$t_{(37)} = -1.81$	0.078
Current comorbid disorder baseline (SCID)					
Mood disorder	6	16		$\chi^2_{(1)} = 5.47$	0.019
Anxiety disorder	2	11		$\chi^2_{(1)} = 6.31$	0.012
Somatoform disorder	1	1		$\chi^2_{(1)} = 0.04$	0.851
Medication					
SSRI/SARI	4	6		$\chi^2_{(2)} = 0.07$	0.791
Benzodiazepines	4	3		$\chi^2_{(1)} = 0.64$	0.425
Antipsychotics	1	1		$\chi^2_{(1)} = 0.04$	0.851
Other	1	2		$\chi^2_{(1)} = 0.14$	0.709
Clinical scores post-treatment					
CAPS total score	21.29 (±14.11)	61.36 (±17.14)		$t_{(37)} = -7.80$	$p < 0.001$
Current comorbid disorder after treatment (SCID)					
Mood disorder	–	4		$\chi^2_{(2)} = 4.43$	0.109
Anxiety disorder	–	7		$\chi^2_{(2)} = 7.78$	0.020
Somatoform disorder	–	1		$\chi^2_{(2)} = 1.63$	0.443
Alcohol dependency	–	2		$\chi^2_{(2)} = 1.71$	0.191
Medication					
SSRI/SARI	3	9		$\chi^2_{(1)} = 3.14$	0.077
Benzodiazepines	3	1		$\chi^2_{(1)} = 1.52$	0.217
Antipsychotics	–	3		$\chi^2_{(1)} = 2.78$	0.096
Other	–	2		$\chi^2_{(1)} = 1.80$	0.180

3.2. PTSD versus controls — baseline associations

Results from the backward regression models ($p < 0.00125$) can be found in the Supplementary information (Supplementary Tables S1–S4). Baseline PTSD was significantly associated with degree and clustering coefficient of a variety of brain regions. Brain areas that were associated with PTSD in the optimal fitted models for at least four thresholds will be discussed below (see Fig. 1 and Table 3).

A positive mean b-value for predicting PTSD group membership was consistently (≥4 thresholds) found for the bilateral olfactory gyrus, right precuneus and left fusiform gyrus. This might indicate that PTSD had on average higher degree in these brain regions compared to controls. A negative mean b-value for predicting PTSD group membership was consistently (≥4 thresholds) found for the degree of the bilateral rolandic operculum, left orbital inferior frontal gyrus, left orbital superior frontal gyrus, right superior temporal gyrus, right inferior temporal gyrus, left angular gyrus, left superior parietal gyrus, left posterior cingulate gyrus, left middle temporal pole, and left pallidum. This might indicate that PTSD had on average lower degree of these brain areas versus controls. The clustering coefficient from the left anterior cingulate cortex was also negatively associated with PTSD for four thresholds. No significant correlations were found between network metrics and symptom severity (CAPS score) at baseline.

3.3. Treatment effects

There were no significant (Bonferroni corrected) group or group by time interaction effects found with the repeated measures ANOVAs ($p < 0.05/16 = 0.003$ is deemed significant). Post-hoc analysis of the remitted versus persistent PTSD patients showed a significant group by time interaction effect of the pallidum degree (threshold 0.4 and 0.5, $p < 0.003$), where remitted PTSD showed an increase in degree or clustering coefficient while persistent PTSD patients did not change over time or showed an increase. No significant correlations were observed between the difference in network metrics and symptom improvement (ΔCAPS).

4. Discussion

In this resting state functional MRI study, baseline PTSD-related functional whole brain network properties were investigated, and followed up after treatment. Prior to treatment, we observed that network topology of orbitofrontal regions, the left cingulate cortex, parietal regions, and temporal regions was associated with PTSD over several thresholds. This indicates that PTSD is associated with aberrant information integration in these brain regions. Longitudinal analyses showed no main effects of group or group by time interaction effects over the course of treatment in these brain regions.

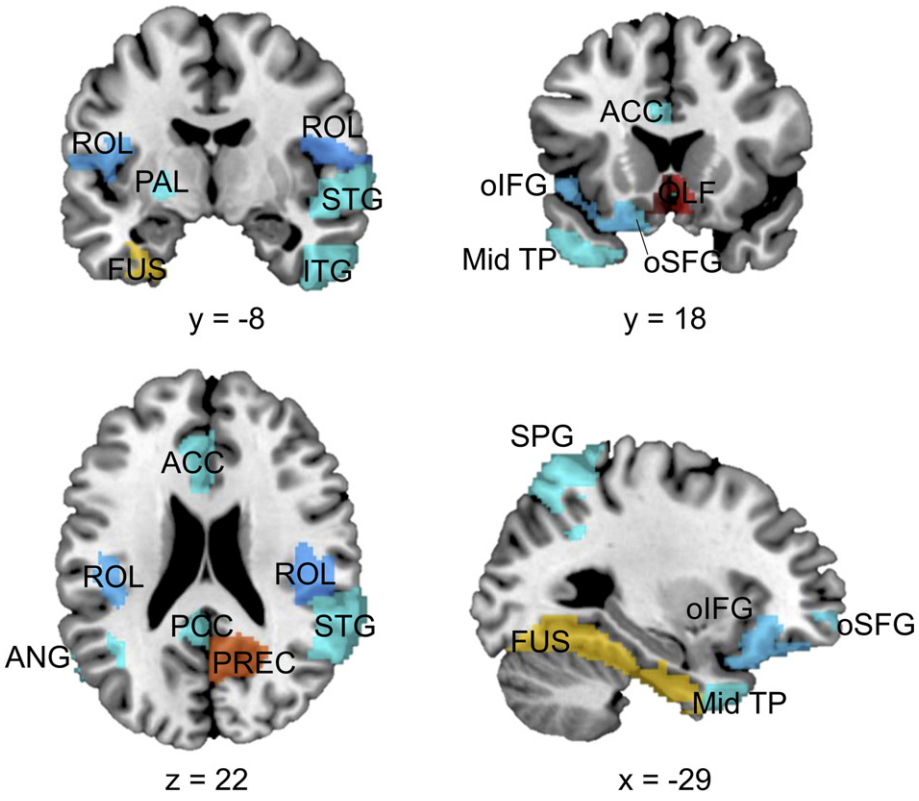

Fig. 1. Brain regions with PTSD-associated clustering coefficient (ACC) and degree (all other regions). Positive associations are presented in warm colors (red, orange), and negative associations in cool (blue) colors. Slices y = −8 & 18; z = 22; z = −29. Abbreviations: ANG = angular gyrus, ACC = anterior cingulate cortex, FUS = fusiform gyrus, ITG = inferior temporal gyrus, Mid TP = middle temporal pole, oIFG = orbital inferior frontal gyrus, OLF = Olfactory gyrus, oSFG = orbital superior frontal gyrus, PAL = pallidum, PCC = posterior cingulate cortex, PREC = precuneus, ROL = rolandic operculum, SPG = superior parietal gyrus, STG = superior temporal gyrus.

Our results are in line with previous cross-sectional resting state whole brain fMRI network studies, reporting decreased orbitofrontal connectivity (Jin et al., 2014), decreased frontal and temporal degree (Suo et al., 2015), and a trend for increased precuneus degree (Lei et al., 2015). A magnetic encephalography (MEG) study also reported increased connectivity of the precuneus (amongst other regions) in PTSD (Dunkley et al., 2014). In addition, a state specific network comprising the cingulate cortex network can differentiate patients from controls (Li et al., 2014). Seed analyses have also shown reduced resting state functional connectivity of the precuneus/posterior cingulate cortex and temporoparietal regions during rest in PTSD patients versus trauma-exposed and non-trauma-exposed controls, which are regions involved in the DMN (Bluhm et al., 2009; Chen and Etkin, 2013; Sripada et al., 2012b). Our results also indicate that DMN regions have reduced degree in PTSD, but on average an increased degree for the precuneus. This indicates that the DMN regions are less integrated in and of less importance for the whole brain network, except for the precuneus, which is more integrated in the whole brain network. The precuneus is involved in autobiographical memory and is also related to self-referential processing (Kelley et al., 2002; Cavanna and Trimble,

Table 3
Frequency of PTSD-associated network metrics of brain regions that were consistently (≥4 thresholds) included in significant optimal fitted backward regression models. The mean, minimum and maximum b-values are also presented for each brain region. On average positive associations (positive mean b-value) with PTSD are presented on the top and on average negative associations (negative mean b-value) on the bottom.

	Lobe	Brain region	Mean b	Min. b	Max. b	Frequency
Positive	Frontal	Right olfactory gyrus	0.240	0.030	0.810	5
		Left olfactory gyrus	0.080	0.060	0.120	4
	Parietal	Right precuneus	0.276	−0.170	1.610	4
	Occipital	Left fusiform gyrus	0.037	−0.194	0.130	4
Negative	Central	Right rolandic operculum	−0.262	−1.020	−0.080	6
		Left rolandic operculum	−0.063	−0.440	0.460	4
	Frontal	Left orbital inferior frontal gyrus	−0.235	−0.460	−0.060	5
		Left orbital superior frontal gyrus	−0.137	−0.178	−0.090	4
	Temporal	Right superior temporal gyrus	−0.098	−0.900	0.200	6
		Right inferior temporal gyrus	−0.106	−0.520	0.260	5
	Parietal	Left angular gyrus	−0.090	−0.160	−0.040	4
		Left superior parietal gyrus	−0.160	−0.290	−0.070	4
	Limbic	Left anterior cingulate gyrus (clustering coefficient)	−0.763	−3.040	2.450	4
		Left posterior cingulate gyrus	−0.294	−0.880	−0.040	4
		Left middle temporal pole	−0.078	−0.110	−0.050	4
	Subcortical	Left pallidum	−0.004	−0.118	0.150	5

2006). Reduced activation of the precuneus has been reported in PTSD patients during encoding of neutral memory (Geuze et al., 2007), while more sensitivity of precuneus to memory formation in an emotional context has also been reported (Whalley et al., 2009). Furthermore, precuneus activity has been related to trauma memory generalization (Hayes et al., 2011), and flashbacks (Whalley et al., 2013). Thus, alterations in the precuneus are associated with PTSD and may potentially be related to altered memory- and self-referential processes, such as memory deficits, intrusions or flashbacks. These findings altogether suggest that the DMN is disturbed in PTSD, and that the number of connections of the precuneus is increased, which warrants further investigation.

Furthermore, we found associations with PTSD in the degree of the pallidum, rolandic operculum, and middle temporal pole, and in the clustering coefficient of the ACC. These are regions that may be regarded as nodes of the salience network (SN; Lei et al., 2015; Menon, 2011). Previous resting state fMRI studies indicated higher functional connectivity between SN brain regions in PTSD versus both trauma-exposed as non-trauma-exposed controls (Daniels et al., 2010; Lei et al., 2015; Sripada et al., 2012b). A structural graph analysis also indicated higher pallidum centrality in PTSD versus non-trauma-exposed controls (Long et al., 2013). This is in line with our results, showing increased importance of the pallidum in the whole brain network. However, other salience network regions had on average lower degree in PTSD (by showing a negative average b-value). This indicates that these regions are less important in the whole brain network in PTSD. Increased connectivity may therefore only be present between specific regions (such as the pallidum) or with limbic brain regions such as the amygdala and the insula, which were regions of interest in the previous resting state studies. Our results do, however, subscribe the importance of SN regions for PTSD. In addition, the average lower clustering coefficient in PTSD observed here suggests that the ACC neighbors have reduced connectivity with each other. This may indicate that information integration in the ACC network is reduced in PTSD. Reduced ACC resting state functional connectivity with the thalamus, amygdala, PCC/precuneus, and prefrontal regions has been reported in PTSD versus non-trauma-exposed controls (Kennis et al., 2014), trauma-exposed controls (Sripada et al., 2012a; Yin et al., 2011) or both (Sripada et al., 2012b). Thus, our results together with previous findings indicate altered connectivity and potentially information processing of the SN is associated with PTSD.

In addition to the DMN and SN, it has been suggested that the central executive network (CEN) is a third important network that can be related to dysfunction in psychiatric disorders, and this model is described as a triple network model (Menon, 2011). Our results support this model by showing an association between PTSD and the degree of important nodes of the CEN, i.e. the superior parietal gyrus, and the orbital part of the IFG and SFG, are associated with PTSD (Menon, 2011). Future studies should investigate if resting state alterations in PTSD are specific to these three networks compared to other networks.

Furthermore, network metrics in the fusiform gyrus and olfactory cortex were on average higher in PTSD, suggesting that these brain areas are more important in the whole brain network in PTSD patients versus controls. Interestingly, altered olfactory perception has been reported in PTSD, which is strongly related to activity of the olfactory cortex (Vasterling et al., 2000; Vermetten et al., 2007; Zald and Pardo, 2000). Furthermore, increased activation of the fusiform gyrus in PTSD versus both trauma-exposed and non-trauma-exposed controls was reported in a meta-analysis (Patel et al., 2012). In addition, previous studies reported higher activity of occipital brain areas in response to trauma-related pictures in PTSD (Hendler et al., 2001; Hendler et al., 2003), and during dissociative responses (Lanius et al., 2005; Whalley et al., 2013). Thus, we could hypothesize that altered network topology of the fusiform gyrus and the olfactory cortex may be related to altered visual and olfactory perception in PTSD, and potentially to dissociative symptoms. However, future research should establish the importance of these brain regions in PTSD.

Although we expected to find differences over the course of treatment between controls, remitted and persistent PTSD, our results did not show any group or group by time interaction effects in the longitudinal analysis. Only when comparing remitted and persistent PTSD patients a significant interaction effect was observed in the pallidum. This indicates that treatment may alter network topology in relation to remission from PTSD, although caution should be taken when interpreting these results. Interestingly, the regions previously related to remission from PTSD or treatment outcome were not associated with PTSD at baseline in our sample (e.g. amygdala, hippocampus, medial PFC; Roy et al., 2010; Simmons et al., 2013; van Rooij et al., 2015a). Alternative approaches (e.g. using treatment-theory driven a priori specified seeds), potentially focusing on pallidum functional connectivity, may provide more sensitivity to treatment related alterations in neural networks.

A number of limitations have to be taken into account when interpreting the findings of this study. First, dividing the PTSD group into a persistent and remitted group resulted in two small samples. However, analyzing the PTSD patient group as a whole did not reveal any general treatment effects, indicating the group subdivision did not underlie the null findings. In addition, by applying whole brain analyses (and not investigating a selection of a priori regions of interest) strong multiple comparison correction was required. Therefore, to confirm that treatment may not alter PTSD-related network metrics, additional research with larger samples of PTSD patients is needed before and after treatment to investigate (heterogeneity in) remission from PTSD. Patients and controls differed on educational level. However, since we did not found correlations with ISCED level and PTSD-related network metrics and their parental education did not differ, educational level is not likely to influence our results. In addition, adding educational level into backward regression (threshold 0.3) did not change the observed association between network metrics and PTSD; similar brain regions remained included in the most optimal fitted model. Thus, although educational level may be lower in PTSD patients, this does not directly interact with the association between brain topology and PTSD. Furthermore, the healthy controls were not followed up after treatment, due to scanner updates. Therefore, including them at baseline may influence the results, especially since the healthy controls differed from the patients in early life trauma. However, exploration of backward regression without the healthy controls showed similar brain regions (threshold 0.3), indicating that the effects were not (fully) driven by inclusion of healthy controls (with lower early life trauma) at baseline. Also, only one female participant applied for this study, and therefore we did not include women here. This hampers generalization of our results to women. The remitted and persistent PTSD group differed in comorbidity. However, there were no significant correlations between PTSD-related network metrics and comorbidity. Therefore, it is not expected that including patients with comorbidity majorly affects our results.

Despite the great care taken to minimize the effects of motion by including regressors (realignment parameters, cerebrospinal fluid signal and white matter signal), the BOLD signal measured to calculate resting state functional connectivity can still be confounded by other temporal patterns, such as cardiac and respiratory patterns, and motion (Van Dijk et al., 2010). Furthermore, we selected only positive connections by starting the thresholding at 0, which may influence our results by introducing a selection bias. However, this was chosen to circumvent interpreting negative correlations, which can be induced by preprocessing steps (Van Dijk et al., 2010). In addition, the methodology to create a neural network representation or connectome is relatively new, is still developing, and has many analytical degrees of freedom (e.g. thresholding, initial parcellation; Drakesmith et al., 2015; Rubinov and Sporns, 2010). Therefore, we presented results of several applied thresholds. Future maturation of the methodology should

provide more standard approaches in order to better compare results between studies.

5. Conclusion

This study indicates that resting state network measures of orbitofrontal, temporal and parietal brain regions, and the cingulate cortex are associated with PTSD. This is in line with previous studies reporting alteration in resting state functional connectivity in the salience network and default mode network. In addition, some regions (orbitofrontal, superior parietal) of the central executive network were also found to be associated with PTSD. Therefore, our results may be interpreted from the triple network model perspective, indicating that indeed the salience, default mode and central executive network are of importance for PTSD psychopathology. However, these PTSD associated network metrics do not seem to change over the course of treatment. This study contributes to a better understanding of the psychopathology of PTSD, and PTSD treatment.

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Conflict of interest

None.

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